Neuron, Vol. 47, 255–266, July 21, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.06.017

Dopamine-Dependent Interactions between Limbic and Prefrontal Cortical Plasticity in the Nucleus Accumbens: Disruption by Cocaine Sensitization

Yukiori Goto* and Anthony A. Grace
Departments of Neuroscience, Psychiatry, and Psychology
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Summary

The prefrontal cortex and the hippocampus exhibit converging projections to the nucleus accumbens and have functional reciprocal connections via indirect pathways. As a result, information processing between these structures is likely to be bidirectional. Using evoked potential measures, we examined the interactions of these inputs on synaptic plasticity within the accumbens. Our results show that the direction of information flow between the prefrontal cortex and limbic structures determines the synaptic plasticity that these inputs exhibit within the accumbens. Moreover, this synaptic plasticity at hippocampal and prefrontal inputs selectively involves dopamine D1 and D2 activation or inactivation, respectively. Repeated cocaine administration disrupted this synaptic plasticity at hippocampal and prefrontal cortical inputs and goal-directed behavior in the spatial maze task. Thus, interactions of limbic-prefrontal cortical synaptic plasticity and its dysfunction within the accumbens could underlie complex information processing deficits observed in individuals following psychostimulant administration.

Introduction

The prefrontal cortex (PFC) and limbic structures, including the hippocampus (HPC) and amygdala, exhibit a number of reciprocal functional interactions that are believed to be mediated via direct and indirect pathways that interconnect these structures (Fuster, 1997). Interaction between these two brain regions has been implicated in a number of cognitive functions (Della-Maggiore et al., 2000; Knight and Grabowecky, 1999; Opitz and Friederici, 2003; Seamans et al., 1998; Simons and Spiers, 2003; Wall and Messier, 2001), and several psychiatric disorders including schizophrenia (Lawrie et al., 2002; Silbersweig and Stern, 1996), depression (Drevets, 2000), and post-traumatic stress disorder (Gilboa et al., 2004) are proposed to result from disruptions in these systems. Excitatory projections from limbic structures are known to activate the PFC (limbic→PFC information flow) (Degenetais et al., 2003), which, in turn, projects to the nucleus accumbens (NAcc), a site at which direct limbic afferents converge (Finch, 1996; French and Totterdell, 2002; Groenewegen et al., 1999). Therefore, the NAcc receives limbic inputs via two sources: direct afferents and indirectly via the PFC (Figure 1A). On the other hand, evidence shows that the PFC may exert an inhibitory influence on limbic structures (PFC→limbic information flow) (Knight and Grabowecky, 1999; Kyd and Bilkey, 2003; Rosenkranz et al., 2003). Therefore, although the PFC would directly drive the NAcc neurons, it would also attenuate limbic inputs into the NAcc (Figure 1A). Thus, the direction of information flow between the PFC and limbic structures is crucial for determining the net effect of PFC and limbic integration as it relates to output selection in the NAcc.

The NAcc is the target of a dopaminergic (DA) innervation arising from the ventral tegmental area (VTA) (Voorn et al., 1986). This afferent system plays a central role in modulating NAcc function and goal-directed behavior (Berridge and Robinson, 1998). We have recently shown that the dynamics of DA release selectively modulate synaptic inputs from the PFC and hippocampus (HPC) via distinct DA receptor subtypes (Goto and Grace, 2005). Thus, basal, tonic DA release determined by the population activity of DA neurons selectively regulates PFC-evoked synaptic drive via D2 receptors, whereas phasic DA release mediated by DA neuron burst spike firing selectively augments HPC inputs into the NAcc via D1 receptor stimulation. However, how these afferent systems interact to impact synaptic plasticity and learned behavior has not yet been elucidated.

Previous studies have shown that HPC activation induces significant DA release in the NAcc (Floresco et al., 2001b). In contrast, PFC activation is reported to decrease DA release within the NAcc (Jackson et al., 2001), most likely via its projection to VTA GABAergic neurons that can suppress VTA-NAcc DA neuronal activity (Laruelle et al., 2003; Sesack and Carr, 2002). Thus, the direction of information flow between the PFC and HPC is also likely to influence DA release in the NAcc. In this study, we examined the mechanism of PFC and HPC information integration and its modulation by DA in the NAcc by giving a high-frequency tetanic stimulation in the HPC and PFC that was sufficient to induce synaptic plasticity in the NAcc (Floresco et al., 2001a; Kombian and Malenka, 1994; Mulder et al., 1997). Although a number of brain regions, including the PFC (Gurden et al., 1999), HPC (Otmakhova and Lisman, 1999), and amygdala (Bissiere et al., 2003), are known to exhibit DA-dependent synaptic plasticity, the influence of DA transmission on synaptic plasticity in the NAcc is controversial (Floresco et al., 2001a; Pennartz et al., 1993; Thomas et al., 2000).

In this study, we found that strong activation of the HPC and PFC produces antagonistic interactions between these afferents in the NAcc with respect to the induction of synaptic plasticity, and moreover, this interaction is controlled in a cooperative manner with respect to the level of D1 and D2 receptor activation. This suggests that not only do the PFC and HPC have opposing effects within the NAcc, but that combined tonic and phasic DA system activation, in addition to differentially regulating afferent drive (Goto and Grace, 2005), appears to influence the balance between PFC

*Correspondence: goto@bns.pitt.edu

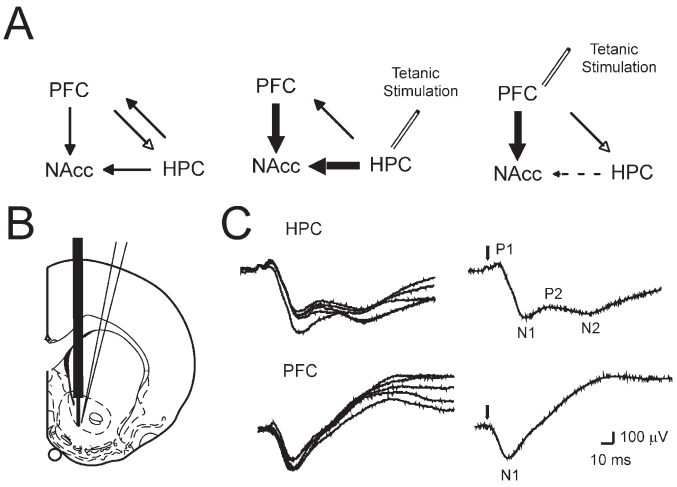

Figure 1. Local Field Potential Responses Evoked in the NAcc by PFC and HPC Stimulation

(A) Diagram illustrating a model of potential pathways that may affect PFC and HPC input interactions in the NAcc. When information flow is from the HPC to the PFC, the NAcc receives coincident PFC and HPC inputs. On the other hand, strong PFC but weak HPC inputs results in suppression of NAcc activity by inhibitory influence of PFC inputs.

(B) Placement of the microdialysis probe and extracellular electrodes within the core region of the NAcc.

(C) Representative traces of HPC- and PFC-evoked responses. Left and right figures show traces of five individual responses and average of ten responses, respectively. HPC-evoked responses consist of a complex of positive and negative shifts (P1, N1, P2, N2). Amplitude was defined as P1 – N1. In contrast, PFC-evoked responses consist of a negative shift followed by a prolonged positive shift. Amplitude was defined as N1 – (baseline measured 1 ms before stimulation).

and HPC synaptic plasticity changes induced in the NAcc. The fact that there is a compromise in these competitive synaptic interactions in cocaine-sensitized animals that correlates with deficits in goal-directed learning suggests that these systems have a significant impact on the way that the balance of synaptic plasticity can affect behavior in pathological conditions.

Results

Synaptic Plasticity at HPC and PFC Afferents

Stimulation electrodes were placed in the ventral HPC (CA1, ventral subiculum) and PFC (prelimbic/infralimbic cortex), and recordings were made primarily from the core, and in some cases the shell, of the NAcc. This was done to evaluate both the direct and indirect interactions mediated by these structures within the NAcc (Figure 1A). Single-pulse stimulation in the HPC and PFC evoked characteristic field potential responses in the NAcc (Figure 1C). Tetanic stimulation (a train of 100 pulses at 50 Hz) delivered to the HPC induced a persistent facilitation of HPC-evoked field potential responses (i.e., long-term potentiation, or LTP; defined as a HPC_{homo}, 45.7% ± 7.9% [mean ± SD] increase measured during the initial 5 min after HPC tetanization relative to baseline average response, n = 9; Figures 2A–2D) simultaneously with a persistent attenuation of PFC-evoked responses (i.e., long-term depression, or LTD; defined as PFC_{hetero}, –34.8% ± 4.7%, n = 9; Figures 2A–2D, Table 1). In all cases, these changes were maintained for more than 30 min. Forty minutes after HPC tetanization, another train of tetanic stimulation was delivered to the PFC. This manipulation induced a persistent depression of HPC_{hetero}-evoked responses as well as an increase in amplitude of PFC_{homo}-evoked responses (HPC_{hetero}, –25.8% ± 2.6% decrease measured during the initial 5 min after a second tetanization relative to an average response for 5 min preceding the second tetanization; PFC_{homo}, 37.4% ± 4.6% increase above baseline following first tetanization, n = 9; Figures 2A–2D, Table 1). When the order of tetanic stimulation was reversed (PFC tetanic stimulation was given first), LTP and LTD induced at HPC (HPC_{homo}, 41.7% ± 7.6%; HPC_{hetero}, –37.9% ± 8.7%; n = 6; Figures 2E and 2F) and PFC (PFC_{hetero}, –30.3% ± 4.4%; PFC_{homo}, 42.5% ± 12.3%) inputs were still similar, suggesting that the order of tetanization is not important for this plasticity. The percent change produced when comparing LTP at HPC_{homo} inputs and LTD at PFC_{hetero} inputs was inversely correlated ($r = -0.91$, $p < 0.01$; Figure 2G), although there was no significant correlation between LTD at HPC_{hetero} inputs and LTP at PFC_{homo} inputs ($r = 0.38$, $p > 0.05$; Figure 2G).

Since HPC stimulation activates PFC neurons, which in turn project to the NAcc (Figure 1A), the P2 component in HPC-evoked responses (Figure 1C) may be mediated by a secondary PFC activation occurring with HPC stimulation. Thus, the alteration of amplitudes defined as P2-N2 in HPC-evoked responses by HPC and PFC tetanic stimulation was examined. It was found that the amplitudes of P2-N2 in HPC-evoked responses were persistently decreased by HPC tetanic stimulation and increased by PFC tetanic stimulation, which was similar to the changes observed with PFC-evoked responses (HPC_{homo}, –24.9% ± 3.6% decrease measured during the initial 5 min after HPC tetanic stimulation relative to the baseline average response; HPC_{hetero}, 29.2% ± 4.3% increase measured during the initial 5 min after PFC tetanic stimulation relative to the average response recorded 5 min preceding the second tetanization, n = 9; Figures 2H and 2I).

DA Modulation of Synaptic Plasticity

To examine the effect of DA on homo- and heterosynaptic plasticity at HPC and PFC inputs into the NAcc, partial DA depletion was conducted using AMPT injection. Four hours after a 300 mg/kg i.p. injection and 2 hr following a second 200 mg/kg injection of AMPT, LTP at HPC_{homo} inputs could not be produced (HPC_{homo}, –2.2% ± 2.1%, n = 7; Figures 3A, 3C, and 3D, Table 1). In addition, instead of producing LTD at PFC afferents by HPC tetanization as observed in con-

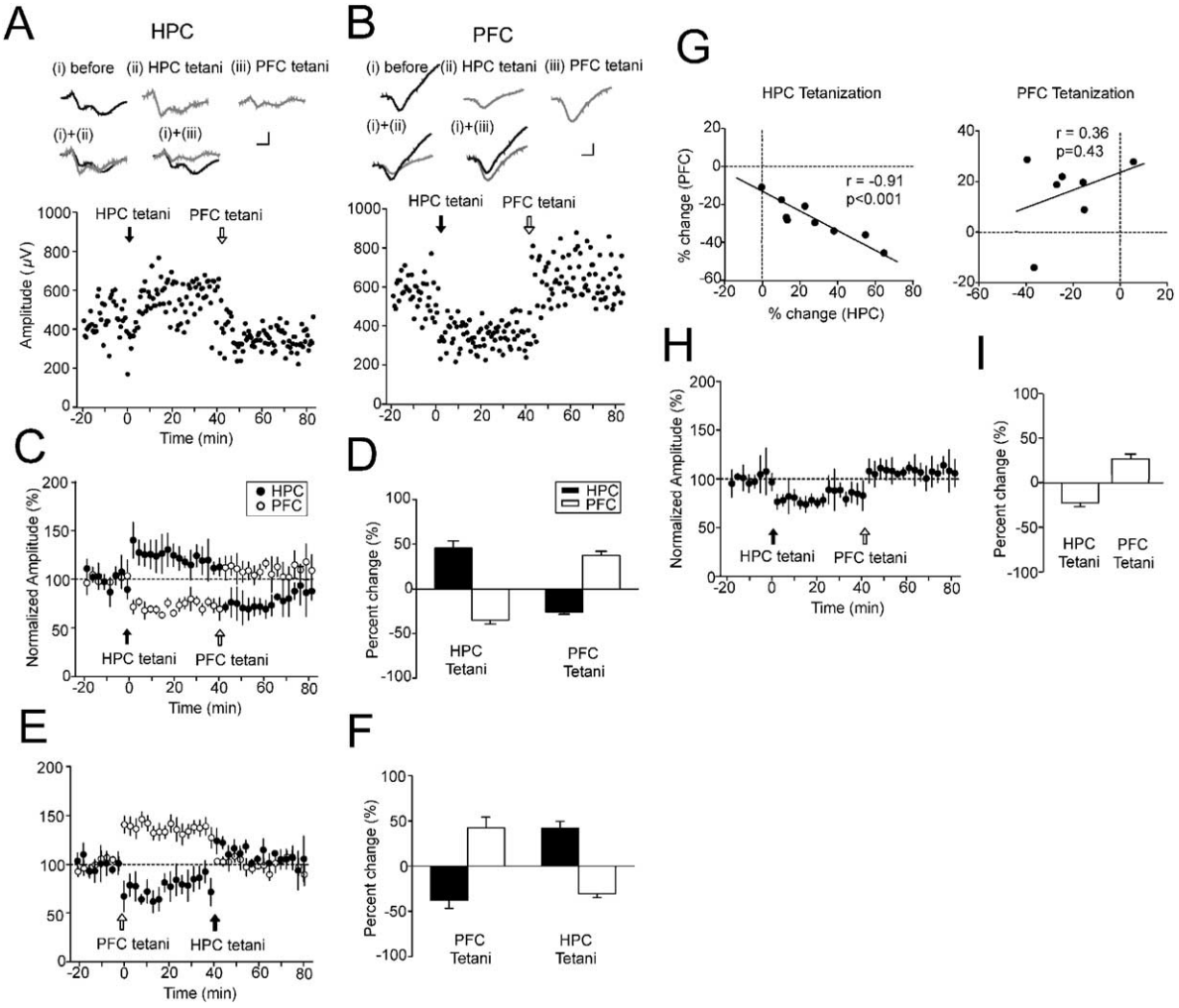

Figure 2. LTP and LTD Were Induced at HPC and PFC Inputs in the NAcc by Tetanic Stimulation in the HPC and PFC

(A) LTP and LTD were induced at HPC inputs following HPC and PFC tetanic stimulation. Black and white arrows indicate the times that HPC and PFC tetanic stimulation were given, respectively. Scale: 0.3 mV and 20 ms.

(B) LTD and LTP were induced at PFC inputs following HPC and PFC tetanic stimulation. Scale: 0.3 mV and 10 ms.

(C) Summary of results showing normalized mean field potential amplitude evoked by HPC (solid circle) and PFC (open circle) test stimuli after tetanic stimulation applied to the HPC (black arrow) and PFC (white arrow). Error bars indicate SD.

(D) Percent change in amplitudes measured 5 min after HPC tetanization compared to baseline responses, or at 5 min after PFC tetanization compared to pre-PFC tetanization baseline.

(E) Summary of results showing normalized mean field potential amplitude evoked by HPC and PFC test stimuli after tetanic stimulation, when the order of HPC and PFC tetanization was reversed.

(F) Percent change in amplitudes for data presented in (E).

(G) Comparison of amplitude changes observed between HPC and PFC inputs reveals a significant correlation between changes in HPC- and PFC-evoked potential amplitude after HPC tetanization, but not after PFC tetanization.

(H) Summary of second component of HPC-evoked potential (P2 – N2) change before and after HPC and PFC tetanic stimulation. Data represent normalized mean field potential amplitude.

(I) Percent change of P2 – N2 in HPC-evoked responses measured 5 min after HPC tetanization compared to baseline responses, or at 5 min after PFC tetanization compared to pre-PFC tetanization baseline.

trol animals, a weak but significant persistent increase (i.e., LTP) was induced in PFC_{hetero}-evoked responses (PFC_{hetero}, 12.3% ± 8.1%, n = 7; Figures 3B–3D, Table 1). In contrast, PFC tetanic stimulation in AMPT-treated animals still induced LTD at HPC_{hetero} inputs (HPC_{hetero}, –31.9% ± 9.3%; n = 7; Figures 3A–3D, Table 1) and LTP at PFC_{homo} inputs (PFC_{homo}, 37.8% ± 6.9%), which was similar to that observed in control rats. These results suggest that DA may be important for synaptic plasticity induced by HPC tetanic stimulation, but not for synaptic plasticity induced by PFC tetanic stimulation. Indeed, HPC stimulation has been shown to induce DA release in the NAcc (Floresco et al., 2001b), suggesting that synaptic plasticity induced by HPC tetanic stimulation is DA dependent.

More detailed mechanisms of DA modulation re-

Table 1. Percentage Change in Amplitudes of Normalized Responses after LTP and LTD Induction

	HPC Tetanization		PFC Tetanization	
Treatment	HPC_{homo}	PFC_{hetero}	HPC_{hetero}	PFC_{homo}
Normal	45.7% ± 7.9%	−34.8% ± 4.7%	−25.8% ± 2.6%	37.4% ± 4.6%
AMPT	−2.2% ± 2.1%*	12.3% ± 8.1%*	−31.9% ± 9.3%	37.8% ± 6.9%
SKF38393	59.5% ± 8.0%	−48.9% ± 4.8%	−31.2% ± 1.1%	42.6% ± 6.3%
SCH23390	2.3% ± 6.5%*	−5.6% ± 7.2%*	−16.6% ± 5.6%	60.5% ± 14.8%
Quinpirole	21.9% ± 2.5%	−20.4% ± 3.5%	−23.6% ± 9.6%	3.9% ± 7.7%*
Eticlopride	24.3% ± 3.7%	24.6% ± 6.9%*	−28.1% ± 1.3%	6.2% ± 5.9%

Mean ± SD. *p < 0.01 compared to normal condition, unpaired t test.

quired for synaptic plasticity induction at HPC and PFC inputs were investigated by local administration of DA agonists and antagonists via a microdialysis probe located adjacent to the site of recordings (Figure 1B). Local administration of the D1 agonist SKF38393 (SKF; 10 μM) produced a significant enhancement of LTP at HPC_{homo} inputs following HPC tetanization (HPC_{homo}, 59.5% ± 8.0%; n = 8; Figures 4A and 4F, Table 1) and LTD at HPC_{hetero} inputs following PFC tetanization (PFC_{hetero}, −48.9% ± 4.8%), but did not affect synaptic plasticity occurring at PFC afferents (PFC_{hetero}, −31.2% ± 1.1%; PFC_{homo}, 42.6% ± 6.3%, n = 8; Figures 4A and 4F, Table 1). Moreover, administration of the D1 antagonist SCH23390 (SCH; 10 μM) blocked induction of LTP at HPC_{homo} inputs (HPC_{homo}, 2.3% ± 6.5%; n = 8; Figures 4B and 4F, Table 1) as well as at PFC_{hetero} inputs (PFC_{hetero}, −5.6% ± 7.2%). In addition, LTD at HPC_{hetero} inputs (HPC_{hetero}, −16.6% ± 5.6%; n = 8; Figures 4B and 4F, Table 1) and LTP at PFC_{homo} inputs (PFC_{homo}, 60.5% ± 14.8%) were moderately attenuated and facilitated, respectively, by the D1 antagonist treatment. In addition, local infusion of NMDA antagonist

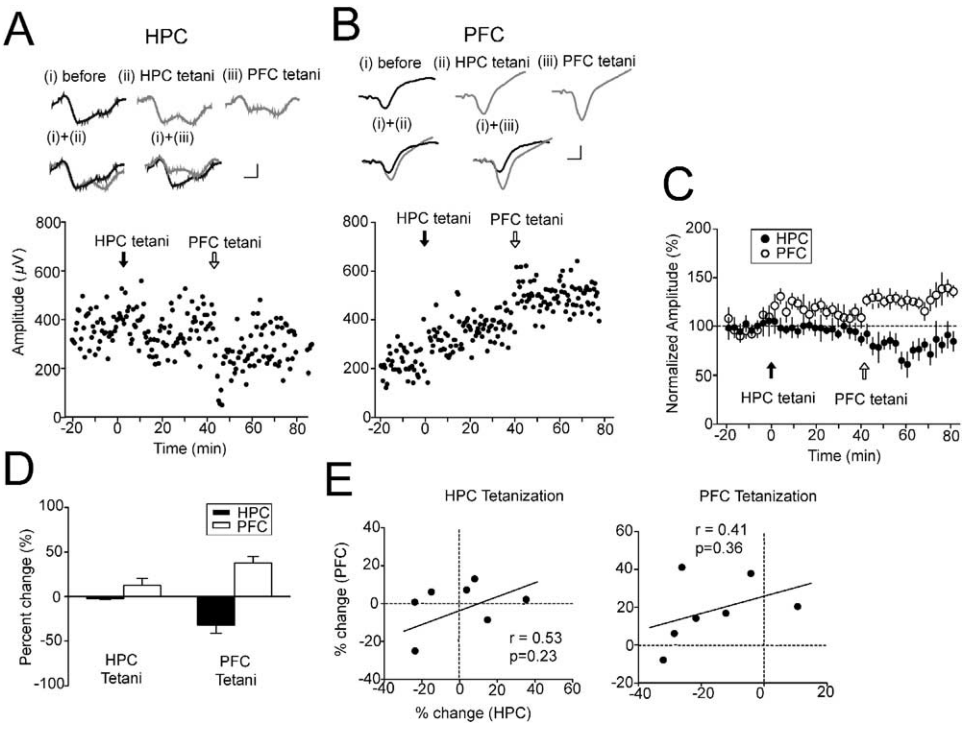

Figure 3. DA Depletion Selectively Alters the Effects of HPC Tetanization on HPC- and PFC-Evoked Responses

(A) Unlike controls, HPC-evoked responses recorded in a DA-depleted rat did not show significant alterations in amplitude following HPC (black arrow) tetanic stimulation, but still showed LTP following PFC (white arrow) tetanization. Scale: 0.1 mV and 20 ms.

(B) PFC-evoked responses recorded in a DA-depleted animal exhibited LTP instead of LTD in control conditions (black arrow), and further persistent increase of amplitude after PFC (white arrow) tetanic stimulation. Scale: 0.1 mV and 20 ms.

(C) Summary of results showing the effects of DA depletion. Data represent normalized mean field potential amplitude evoked by HPC (solid circle) and PFC (open circle) test stimuli. Error bars indicate SD.

(D) Percent change in amplitudes measured 5 min after HPC tetanization compared to baseline responses, or at 5 min after PFC tetanization compared to pre-PFC tetanization baseline.

(E) Following DA depletion, the correlation between HPC and PFC inputs following HPC tetanization was lost, suggesting that DA may mediate the balance of synaptic plasticity changes between HPC and PFC inputs.

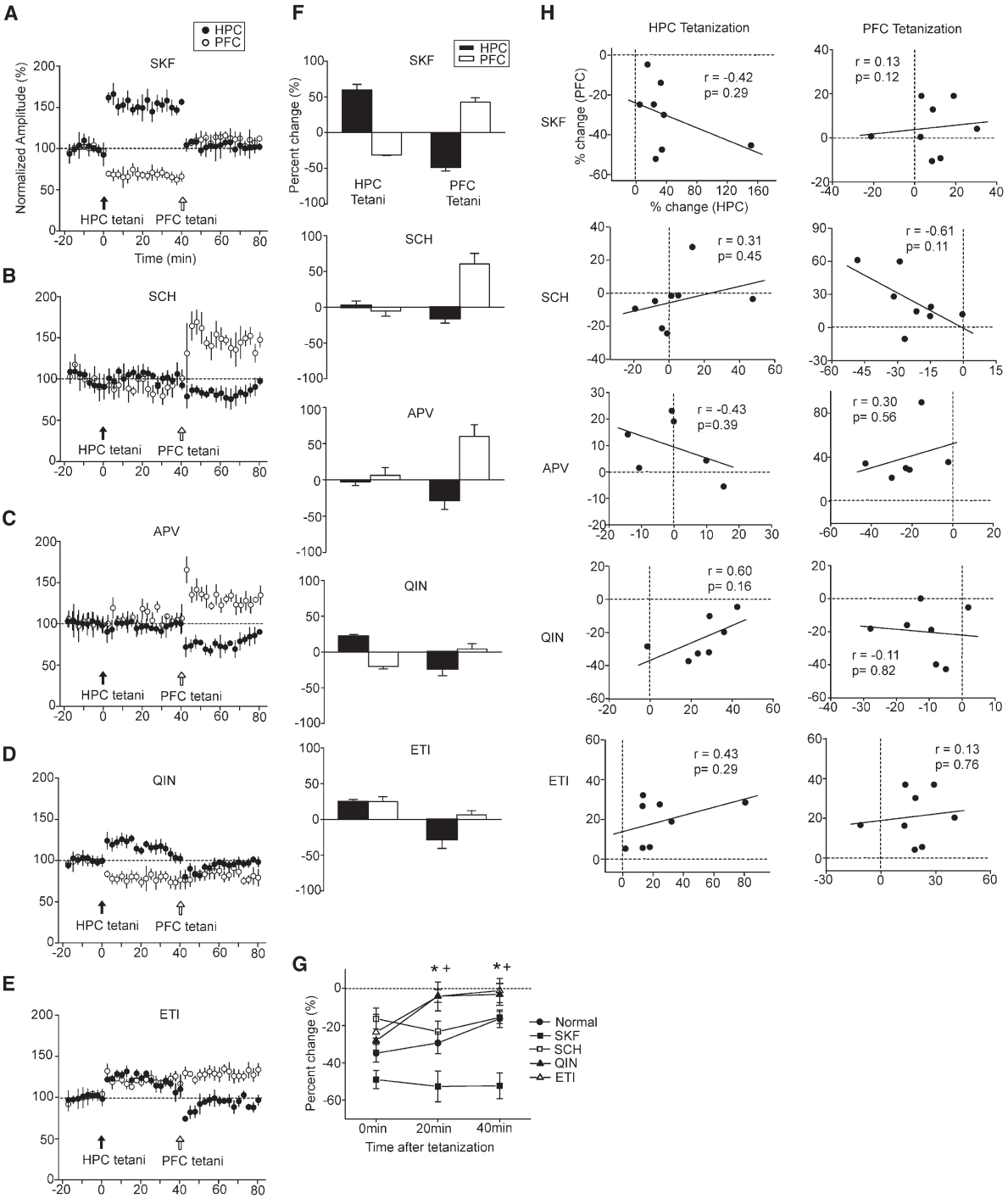

Figure 4. DA D1 and D2 Receptors Selectively Modulate Synaptic Plasticity at HPC and PFC Inputs, Respectively

(A–D) Evoked potentials recorded from HPC (solid circle) and PFC (open circle) stimulation in response to HPC (black arrow) and PFC (white arrow) tetanization following local application of D1 agonist ([A]; SKF38393, SKF), D1 antagonist ([B]; SCH23390, SCH), NMDA antagonist ([C]; AP-V), D2 agonist ([D]; quinpirole, QIN), and D2 antagonist ([E]; eticlopride, ETI). Error bars indicate SD.

(F) Percent change in amplitudes of the normalized responses shown in (A)–(D). Only the HPC-evoked plasticity appears to be dependent on NMDA receptor stimulation.

(G) Analysis of the time course of responses reveals the significantly faster decays of synaptic depression following PFC tetanization only at HPC inputs during D2 agonist and antagonist treatments. (*, $^{+}$: $p < 0.05$ for QIN and ETI compared to control condition, two-way ANOVA).

(H) In the presence of DA agonists and antagonists, the correlation between HPC and PFC synaptic plasticity following HPC tetanization was lost.

AP-V (50 μM) into the NAcc also disrupted LTP at HPC_{homo} (–3.1% ± 4.5%) and LTD at PFC_{hetero} (6.4% ± 10.4%) inputs, but not with respect to the other stimulation contingencies (HPC_{hetero}, –28.8% ± 11.9%; PFC_{homo}, 59.9% ± 15.9%; n = 6; Figures 4C and 4F), suggesting that enhanced Ca^{2+} influx into the cell by D1-NMDA synergism (Greengard et al., 1999) may be involved in synaptic plasticity induced by HPC tetanic stimulation, whereas LTD at HPC_{hetero} and LTP at PFC_{homo} inputs are NMDA independent.

Local administration of the D2 agonist quinpirole (QIN; 10 μM) resulted in a blockade of LTP induction at PFC_{homo} inputs (HPC_{homo}, 21.9% ± 2.5%, PFC_{hetero}, –20.4% ± 3.5%, HPC_{hetero}, –23.6% ± 9.6%, PFC_{homo}, 3.9% ± 7.7%, n = 7; Figures 4D and 4F, Table 1). On the other hand, the most striking effect produced by administration of the D2 antagonist eticlopride (ETI; 20 μM) was a reversal in the polarity of the synaptic plasticity induced at PFC_{hetero} inputs by HPC tetanic stimulation; i.e., LTP was induced instead of the LTD that was observed in control conditions (HPC_{homo}, 24.3% ± 3.7%, PFC_{hetero}, 24.6% ± 6.9%, HPC_{hetero}, –28.1% ± 1.3%, PFC_{homo}, 6.2% ± 5.9%, n = 8; Figures 4E and 4F, Table 1). In addition, D2 receptor modulation also caused short-term changes in synaptic plasticity. Thus, the synaptic depression at HPC_{hetero} inputs produced following administration of either the D2 agonist or antagonist was of significantly shorter duration (i.e., short-term depression) than that observed in the normal condition with the depression present for only 10–20 min following tetanization. No alteration in the degree of initial attenuation of HPC_{hetero}-evoked responses immediately after PFC tetanic stimulation was observed (basal, –29.3% ± 5.9% at 20 min, –16.3% ± 4.7% at 40 min; SKF, –42.6% ± 8.3% at 20 min, –42.3% ± 6.9% at 40 min; SCH, –22.3% ± 5.6% at 20 min, –15.7% ± 3.2% at 40 min; QIN, –4.4% ± 7.8% at 20 min, –1.3% ± 6.4% at 40 min; ETI, –4.2% ± 3.4% at 20 min., –3.3% ± 5.9% at 40 min; two-way ANOVA, $p < 0.05$ for QIN and ETI at time 20 min and 40 min compared to normal condition; Figure 4G). These data suggest that long-term stabilization of the synaptic depression at HPC_{hetero} inputs following PFC tetanization is dependent on tonic D2 receptor-mediated activity.

Synaptic Plasticity in the NAcc Shell

Because of the demonstrated relevance of the NAcc shell to the actions of drugs of abuse (Robinson and Kolb, 1999; Thomas et al., 2001), we also examined plasticity within this subregion of the NAcc. LTP and LTD induced at HPC and PFC inputs in the shell of the NAcc in saline-treated animals were similar to those induced in the core, although the polarity of field responses was opposite between the core and the shell of the NAcc (see Figure 6B). Nonetheless, given the possibility that a difference in DA dependence of synaptic plasticity may be present in the shell, we repeated the LTP and LTD induction in the shell with DA manipulation by SCH and QIN, which have been shown to block LTP at HPC_{homo} and LTD at PFC_{hetero} inputs induced by HPC tetanic stimulation and LTP at PFC_{homo} inputs induced by PFC tetanic stimulation, respectively, in the core (Figures 4B and 4D). SCH pretreatment blocked LTP at HPC_{homo} (–3.9% ± 14.0%; n = 6; Figures 5A and 5C) and LTD at PFC_{hetero} (1.2% ± 7.9%) inputs in shell, but did not affect LTD at HPC_{hetero} (HPC_{hetero}, –42.0% ± 10.4%) and LTP at PFC_{homo} inputs (PFC_{homo}, 52.1% ± 11.3%). In addition, QIN selectively disrupted LTP at PFC_{homo} inputs (HPC_{homo}, 44.5% ± 12.1%; PFC_{hetero}, –35.0% ± 5.1%; HPC_{hetero}, –38.7% ± 10.8%; PFC_{homo}, 1.7% ± 0.7%; n = 6; Figures 5B and 5D). The correlation coefficient of these changes between the core and shell across different manipulations was almost unity ($r = 0.94$, $p < 0.01$), suggesting that the patterns of responses with respect to LTP and LTD in the core and shell with normal, SCH, and QIN conditions are essentially identical (Figures 5E and 5F). These results suggest that DA-dependent synaptic plasticity in the shell is similar to that in the core of the NAcc.

Altered Plasticity and Goal-Directed Behavior following Cocaine Sensitization

Recent studies have suggested that at least some of the indices of drug addiction may be dependent on abnormal synaptic plasticity induction within the mesolimbic DA system (Kolb et al., 2003; Robinson and Kolb, 1999; Thomas et al., 2001). However, the results of studies into synaptic plasticity in the NAcc of animals exhibiting behavioral sensitization to psychostimulants have been inconsistent. For example, LTD was found at the cortical inputs within NAcc in brain slices prepared from sensitized animals (Thomas et al., 2001). On the other hand, NAcc neurons from drug-sensitized animals have been reported to exhibit an increase in dendritic spines (Robinson and Kolb, 1999), which would be more predictive of LTP rather than LTD. Thus, we investigated whether PFC and HPC synaptic plasticity was altered in animals that exhibited behavioral sensitization to cocaine. Repeated daily cocaine treatment (15 mg/kg, i.p.; cocaine group) in animals induced a progressive increase in the locomotor responses to the drug (Figure 6A), whereas repeated daily saline treatment (1.0 ml; saline group) did not. Ten to 17 days following the last injection of cocaine or saline, a 15 mg/kg challenge dose of cocaine was administered to both groups of rats. The cocaine-sensitized group exhibited significantly greater drug-induced locomotion to a challenge injection of cocaine than that observed in the last dose administered during repeated cocaine treatment (cocaine group, 4792 ± 499 cm at 6th day of cocaine treatment, 7336 ± 668 cm to challenge injection, $p < 0.01$, paired t test, n = 10), demonstrating the presence of behavioral sensitization. Between 1 to 5 days following this evaluation, the rats were subjected to electrophysiological recordings. Based on previous studies (Robinson and Kolb, 1999; Thomas et al., 2001), recordings were made from neurons within the shell of the NAcc. In saline-treated control rats, HPC tetanic stimulation induced LTP at HPC_{homo} inputs (HPC_{homo}, 38.3% ± 7.5%; n = 6; Figures 6C and 6D) and LTD at PFC_{hetero} inputs (PFC_{hetero}, –27.6% ± 7.4%) in the NAcc shell. However, in the cocaine-sensitized rats, HPC tetanic stimulation failed to induce any persistent change in the HPC_{homo}- and PFC_{hetero}-evoked responses (HPC_{homo}, 1.2% ± 5.3%; PFC_{hetero}, –3.2% ± 5.2%; $p < 0.01$ compared to the saline group; n = 10; Figures 6C

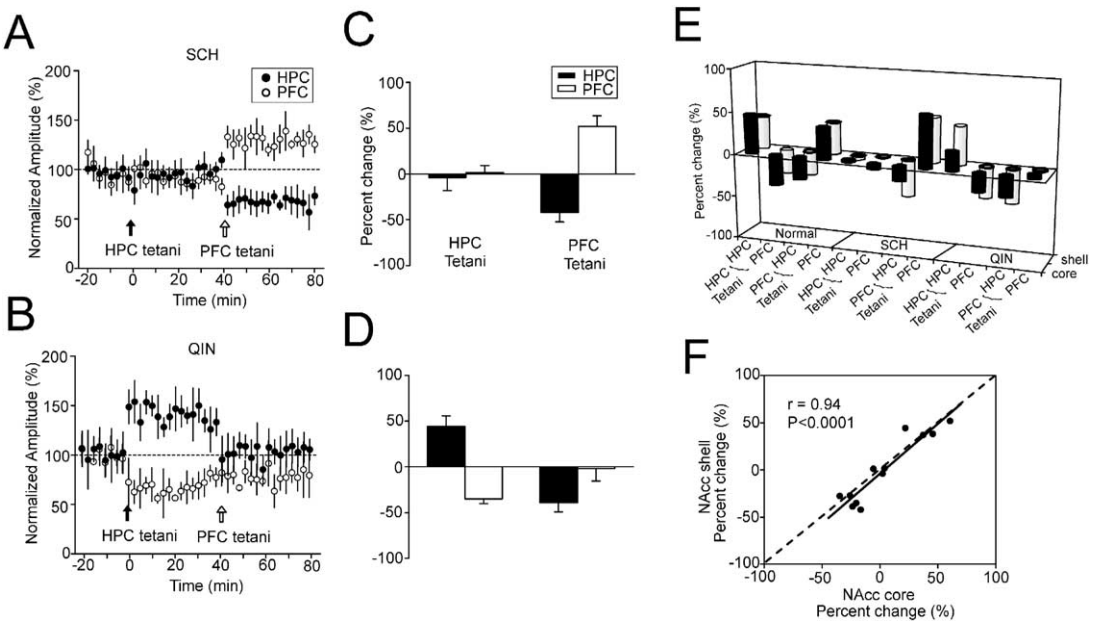

Figure 5. DA Dependence of Synaptic Plasticity Induced in the Shell Is Similar to that Observed in the Core of the NAcc

(A and B) Evoked potentials recorded from HPC (solid circle) and PFC (open circle) stimulation in response to HPC (black arrow) and PFC (white arrow) tetanization following local application of D1 antagonist and D2 agonist, respectively. Error bars indicate SD.

(C and D) Percent change in amplitudes of the normalized responses shown in (A) and (B).

(E) Comparison of percent changes of responses with LPT and LTD between the NAcc core and shell in normal, SCH, and QIN conditions. Percent changes in normal condition in the shell are taken from those in saline-treated animals shown in (C) and (D).

(F) Correlation of percent changes between the NAcc core and shell across different conditions; each point represents comparison from one condition derived from (E). Percent changes occurring at HPC and PFC inputs with HPC and PFC tetanic stimulation in normal condition and with SCH and QIN in the NAcc core (x axis) are plotted against those in the shell (y axis).

and 6D). On the other hand, synaptic plasticity induced by PFC tetanization was not different when comparing the cocaine and saline groups (cocaine group, HPC_{hetero}, –27.2% ± 8.4%; PFC_{homo}, 37.3% ± 6.5%; n = 10; saline group, HPC_{hetero}, –21.9% ± 5.2%; PFC_{homo}, 30.6% ± 4.1%; n = 6; Figures 6C and 6D).

We also tested whether this synaptic alteration induced by cocaine sensitization was reflected by disruption of goal-directed behavior. Using a plus-maze task, we tested learning and set shifting of response strategies. In these tasks, rats were required to make turns in order to obtain rewards, with the turning direction based on either a visual cue placed in the maze (visual cue task, or VCT) or response direction (response direction task, or RDT). After reaching response criterion (ten consecutive correct responses in a session) in VCT, the task was switched to RDT until criterion performance level was again reached. We have shown previously that HPC inactivation combined with D1 receptor blockade in the NAcc interferes with acquisition of both tasks, whereas PFC inactivation combined with D2 receptor stimulation selectively disrupts task switching (Goto and Grace, 2005).

Control saline-treated rats (n = 6) required 55.8 ± 5.1 trials in VCT and 61.0 ± 3.7 trials in RDT to reach criterion (Figure 6E). Perseverative and regressive errors were 6.3 ± 0.8 and 6.2 ± 0.8 trials, respectively (Figure 6E). On the other hand, cocaine-sensitized rats (n = 6) required a significantly smaller number of trials to reach criterion in VCT compared to control animals (42.5 ± 4.2 trials; $p < 0.05$), but not in RDT (62.2 ± 3.7 trials, Figure 6E). However, perseverative and regressive errors in cocaine-sensitized rats were significantly increased and decreased, respectively (perseverative errors, 10.2 ± 0.7 trials; regressive errors, 3.2 ± 0.8 trials; Figure 6E). These increased perseverative and decreased regressive errors are counterbalanced in RDT, resulting in no difference in the number of trials taken in RDT between control and cocaine-sensitized rats. These results suggest that the learning of a response strategy is facilitated, whereas switching of a strategy in goal-directed behavior is disrupted by cocaine sensitization, perhaps because of the influence of perseveration on task performance.

Discussion

In this study, we show that (1) PFC and HPC inputs have mutually opposing interactions within the NAcc that affect synaptic plasticity in a manner that is determined by the direction of information flow between these structures, (2) PFC and HPC synaptic plasticity is selectively modulated via D1 and D2 receptors, and (3) repeated treatment with a psychostimulant disrupts this synaptic plasticity. In a previous study (Goto and Grace, 2005), we showed that tonic and phasic DA transmission independently affect PFC and HPC inputs into the NAcc via D2 and D1 receptors, respectively.

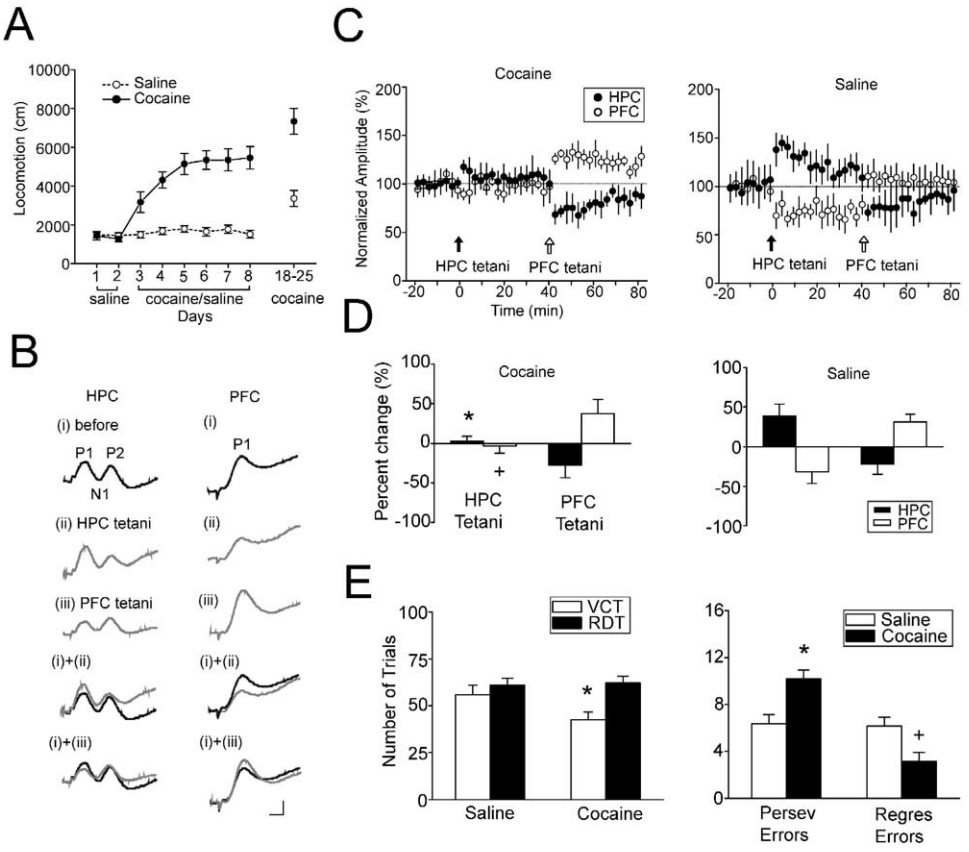

Figure 6. Repeated Cocaine Treatment Disrupts Synaptic Plasticity within the NAcc

(A) Repeated cocaine administration caused behavioral sensitization to a challenge dose of cocaine injection (15 mg/kg) administered 10–18 days following withdrawal. Error bars indicate SD.

(B) HPC- and PFC-evoked responses recorded in the NAcc shell from saline-treated animals. Amplitudes in both HPC- and PFC-evoked responses were defined as P1 – (baseline measured 1 ms before stimulation). Scale: 0.3 mV and 20 ms.

(C) In rats showing behavioral sensitization to cocaine treatment, the effects of HPC tetanization were strongly attenuated (left). On the other hand, no such alteration was observed in saline-treated control rats (right). Data represent normalized mean field potential amplitude evoked by HPC (open circle) and PFC (solid circle) test stimuli after HPC (black arrow) and PFC (white arrow) tetanization.

(D) Percent change in amplitudes for 5 min after HPC tetanization compared to baseline responses or at 5 min after PFC tetanization compared to pre-PFC tetanization baseline. The percent change in amplitude of HPC_{homo} and PFC_{hetero} inputs in the cocaine group are significantly reduced when compared to the saline group (*, $^{+}$: $p < 0.01$, unpaired t test).

(E) Left graph shows the number of trials that cocaine-sensitized and saline control rats took to reach criterion in the visual cue task (VCT) and response direction task (RDT). The number of trials required to reach criterion in cocaine-sensitized animals is significantly less than controls in VCT (*, $p < 0.05$ compared to saline-treated animals). Right graph shows that perseverative and regressive errors are significantly increased and decreased, respectively, in cocaine-sensitized animals (*, $^{+}$, $p < 0.05$ compared to saline-treated animals). Persev and Regres denote perseverative and regressive errors, respectively.

We have now shown that PFC and HPC inputs exhibit antagonistic interactions with respect to the induction of synaptic plasticity in the NAcc, and this interaction is strongly influenced by the level of coactivation of D1 and D2 DA receptors. Furthermore, interference with DA dynamics by cocaine sensitization produces synaptic plasticity impairments that correlate with deficits in goal-directed behavior. Taken together, the results suggest that, during HPC activation, increased tonic and phasic DA transmission activates D1 and D2 receptors to shift the balance of information flow in the NAcc from PFC to HPC by facilitating LTP at HPC inputs and LTD at PFC inputs. On the other hand, when the PFC is active, an interruption of tonic D2 receptor stimulation (e.g., via decreased DA neuron firing [Floresco et al., 2003] or administration of an antipsychotic drug) would facilitate LTP at PFC inputs and LTD at HPC inputs, thereby reversing the effects produced by phasic activation of the DA system.

The NAcc receives massive DA projections from the VTA. Although DA is known to be essential for induction of synaptic plasticity in many brain regions, including the PFC (Gurden et al., 1999), HPC (Otmakhova and Lisman, 1999), amygdala (Bissiere et al., 2003), and the dorsal striatum (Calabresi et al., 1992), it has been suggested that synaptic plasticity in the NAcc may occur independent of its DA innervation (Hyman and Malenka, 2001; Kombian and Malenka, 1994; Pennartz et al., 1993; Wise, 2004). It is important to note that these latter experiments were conducted in a brain slice prepa-

ration where DA release is substantially different from that occurring in vivo (i.e., less spontaneous tonic DA release) and that the stimulation of afferents was done by placing electrodes on the cortical afferents into the NAcc. Our results could explain this apparent contradiction. Thus, we have shown here that LTP at PFC inputs is produced only when there is a decrease in tonic D2 receptor stimulation. However, in the slice preparation (in which disconnection of DA afferents from cell bodies in the VTA would decrease tonic DA stimulation), the lack of D2 activation would cause the induction of LTP at unidentified cortical (but not HPC) inputs to appear as DA independent. Thus, the inability to selectively stimulate afferents and the diminished tonic D2 stimulation present in the in vitro brain slice is likely to provide misleading results regarding the role of DA in synaptic plasticity in the NAcc. Another factor is that stimulation in slice preparations is typically delivered to the fibers in the corpus callosum rather than on specific cortical cell bodies, and such stimulation may lead indirectly to DA release in the NAcc (e.g., Pennartz et al., 1993; Thomas et al., 2001). As a result, the potential callosum-evoked DA release may produce confound results obtained in an in vitro preparation. DA clearly plays a selective role in the modulation of synaptic plasticity within the NAcc.

Our data show that LTP at HPC_{homo} inputs are blocked by the D1 antagonist, suggesting that D1 receptor activation by phasic DA release is crucial for this to occur, with this interaction being mediated by a postsynaptic action of D1 stimulation (Goto and Grace, 2005). Indeed, it has been shown that D1 receptor stimulation facilitates Ca^{2+} influx into NAcc neurons secondary to NMDA channel phosphorylation (Greengard et al., 1999). In addition, LTD may be induced at PFC_{hetero} inputs via NMDA-dependent activation of NO (Stanton et al., 2003), which could be one mechanism responsible for altering the D2-dependent modulation of PFC neurotransmission (Figures 7A and 7B) (Bamford et al., 2004; O'Donnell and Grace, 1994). On the other hand, PFC tetanic stimulation induces LTP at PFC_{homo} inputs, and this form of plasticity is disrupted by D2 receptor stimulation. Although the precise mechanism for this interaction remains to be established, since D2 receptors are stimulated by basal, tonic DA release due to their high affinity for DA (Grace, 1991; Hall et al., 1985), a suppression of DA release would decrease D2 receptor stimulation, which would in turn decrease D2-mediated attenuation of glutamate release from PFC terminals via a presynaptic action (Bamford et al., 2004; O'Donnell and Grace, 1994). This increased glutamate release may then facilitate LTP induction (Figures 7C and 7D). Indeed, our study suggests that PFC activity is crucial for induction of LTP and LTD on PFC afferents into the NAcc. Thus, when activity in some cortical neurons is weak, then DA would not be expected to alter plasticity on such afferents. This is consistent with a recent finding that weaker cortical inputs are less influenced by D2-dependent dopamine stimulation (Bamford et al., 2004).

Repeated cocaine treatment induced an alteration in synaptic plasticity in the NAcc shell. There are several potential mechanisms that may account for this alteration. For example, these results are consistent with

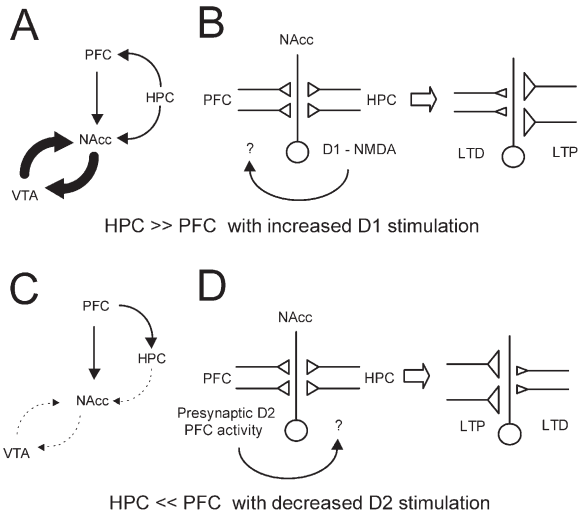

Figure 7. A Proposed Mechanism for DA Modulation of Synaptic Plasticity at HPC and PFC Inputs in the NAcc

(A and B) When HPC activity is stronger than PFC activity, the direction of information flow is from the HPC→PFC. In this condition, NAcc activity is enhanced with coincident HPC and PFC inputs into this region, which would produce an overall increase in DA release into the NAcc via suppression of VP inhibitory action on DA neurons (Floresco et al., 2003). In the presence of increased phasic DA release, D1 receptor stimulation enhances NMDA-mediated Ca^{2+} influx into NAcc neurons to induce LTP at HPC inputs (Greengard et al., 1999). The D2-dependent induction of LTD at PFC inputs could occur via several mechanisms, including second messenger systems or possibly production of NO (Stanton et al., 2003) through NMDA receptor activation.

(C and D) On the other hand, when PFC activity is stronger than HPC activity, the direction of information flow is from the PFC→HPC. In this condition, NAcc activity is suppressed (Goto and O'Donnell, 2002), which in turn disinhibits the VP and decreases tonic DA release in the NAcc. In instances where there is a reduction of tonic DA release, the resultant decrease in D2 receptor stimulation would enhance PFC afferent stimulation of the NAcc; this may facilitate LTP induction at PFC inputs.

the hypothesis that repeated cocaine may have induced a pre-existing LTP at HPC inputs, possibly by increasing the number of synaptic inputs from limbic structures (Robinson and Kolb, 1999) or via a disruption of the cellular mechanisms responsible for the induction of synaptic plasticity in NAcc neurons, such as D1-NMDA interactions and activation of second-messenger cascades (Greengard et al., 1999) that could regulate AMPA receptor trafficking (Mangiavacchi and Wolf, 2004). Alternately, the LTD at cortical inputs may involve a decreased glutamate release from PFC terminals that was not further modulated by HPC tetanic stimulation, although no change has been reported in paired-pulse ratio at the cortico-NAcc pathway with LTD in cocaine-sensitized animals, suggesting possible involvement of postsynaptic mechanism (Thomas et al., 2001). Whether the alteration is due to presynaptic or postsynaptic mechanisms, or a combination of both, remains to be determined.

The results suggest that when the primary drive originates in limbic structures (limbic→PFC information flow), the subsequent information processing in the

NAcc shifts in favor of limbic structures due to the induction of LTP at limbic inputs and LTD at PFC inputs that is dependent on increased D1/D2 receptor activation. On the other hand, when the PFC is more highly activated (PFC→limbic information flow), information processing in the NAcc is shifted toward a PFC predominance due to induction of LTD at limbic inputs and LTP at PFC inputs; this shift is driven by a reduction in D1/D2 receptor stimulation. Thus, we propose that when D1 and D2 receptors are coactivated by increases in phasic and tonic DA release, respectively (Goto and Grace, 2005), there is a shift toward limbic predominance, with decreases in tonic and phasic DA transmission shifting synaptic plasticity and information processing in favor of the PFC. Therefore, the recent history of input activation and the current states of the DA system potently determine which set of inputs will control subsequent information flow. This model is supported by the results of our behavioral experiments. We have recently shown that, using the same spatial maze test paradigm, learning and set shifting are mediated by D1-dependent limbic-NAcc and D2-dependent PFC-NAcc information processing, respectively (Goto and Grace, 2005). We propose that the synaptic plasticity induced at HPC and PFC inputs into the NAcc shown in this study may mediate these different aspects of goal-directed behavior. Therefore, LTP at HPC inputs and LTD at PFC inputs, combined with reward-related DA release (Schultz, 1998), may be important for learning a response strategy. In contrast, LTP at PFC inputs and LTD at HPC inputs could reverse this learning to shift to a different response strategy, as may occur with the transient suppression of DA release secondary to the omission of an expected reward (Schultz, 1998). Cocaine-sensitized rats exhibited a significantly larger number of perseverative errors at task switching. PFC damage is known to lead to perseverative errors (Milner, 1963). Thus, in the cocaine-sensitized rats, PFC influence may be disrupted via an insufficient PFC-driven suppression of NAcc activity (Goto and O'Donnell, 2002) secondary to abnormal induction of LTD at PFC inputs. On the other hand, cocaine-sensitized rats exhibited faster learning of a response strategy. This may also reflect perseveration, in that once the drug-sensitized animals acquire a response strategy, they may perseverate on this response without testing other possible strategies, as evidenced by the smaller number of trials taken in VCT and decreased regressive errors in RDT in cocaine-sensitized rats. Thus, although abnormally induced LTP by psychostimulants at limbic inputs might not interfere with learning a response strategy, it may reduce the capacity of these animals to consider alternate response strategies. In this way, the disruption of synaptic plasticity by cocaine sensitization may contribute to the affective- and context-inappropriate impulsive behaviors that are characteristics of drug addiction (Ciccocioppo et al., 2001; Jentsch and Taylor, 1999; Vorel et al., 2001).

Experimental Procedures

Recording

All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

In vivo field potential recordings were done in adult male Sprague-Dawley rats (265–440 g, n = 87). Rats were anesthetized with chloral hydrate (400 mg/kg) and placed in a stereotaxic apparatus. Extracellular field potential electrodes pulled from glass micropipettes and filled with 2 M NaCl were lowered into the lateral shell or medial core regions of the NAcc at a 10° angle (Figure 1B). Field potential signals were amplified 1000 times with an AC amplifier and band-pass filtered at 0.1–100 Hz. Recordings were digitized with an interface board at 10 kHz and fed to a computer for offline analysis. All data handling was performed using custom software (Neuroscope).

Concentric bipolar stimulation electrodes were placed in the HPC (ventral CA1/subiculum) and PFC (prelimbic/infralimbic cortex). Single current pulses (0.2 ms; 0.2–1.0 mA) were delivered every 30 s alternately to the HPC and PFC. Current intensity was adjusted to evoke approximately 60%–70% of maximal responses. LTP and LTD were induced with high-frequency stimulation consisting of a train of 100 pulses at 50 Hz (1.0 mA).

Data Analysis

LTP and LTD were defined as a statistically significant ($p < 0.05$, repeated measures ANOVA) increase or decrease in the field potential amplitude that was maintained for at least 30 min after tetanic stimulation.

Drug Administration

DA agonists and antagonists were administered via reverse microdialysis at a concentration found to be selective for D1 and D2 receptor activation and blockade (West and Grace, 2002). The probes were located within 500 μm of the tip of the recording electrodes. Dialysis probes (2 mm exposed membrane) were advanced into the NAcc slowly at the rate of 3–5 μm/s to minimize any damage to the brain tissues. All drugs were dissolved in artificial cerebrospinal fluid (aCSF; SKF38393, 10 μM; SCH23390, 10 μM; quinpirole, 10 μM; eticlopride, 20 μM; AP-V, 50 μM). aCSF was continuously perfused throughout the experiments and switched to drug administration 20 min before recordings were started. Drug perfusions were continued until the termination of the recording session. DA depletion was done by intraperitonial injection of AMPT (300 mg/kg, 4 hr before plus 200 mg/kg 2 hr before recording).

Cocaine Sensitization

Rats received either daily saline (1.0 ml) or cocaine (15 mg/kg, dissolved in 1.0 ml saline) injection intraperitoneally. Immediately following injection, horizontal locomotor activity was measured for 20 min in an open-field chamber. The cocaine group received 2 days of saline injection followed by 6 days of one-per-day cocaine treatment, and the saline group received 8 days of saline injections. Following 10–18 days of withdrawal from cocaine, both groups received a challenge cocaine injection (15 mg/kg), and locomotion was assessed. Recordings were conducted between 1 to 5 days following the challenge test.

Cross-Maze Tests

Strategy learning and response switching in goal-directed behavior were tested in rats that had been sensitized to cocaine and those that had received saline. This task employed a visual cue-directed task (VCT) and a response direction task (RDT) using a cross-maze paradigm as described in other studies (Goto and Grace, 2005; Ragozzino et al., 2002).

After animals completed locomotor measurements with challenge injection of cocaine, the rats were subjected to 3 days of intensive handling (10 min each day) and another 3 days of habituations to the maze. During handling and maze habituation, animals were food-restrained to maintain about 85% of body weight compared to the normal condition.

VCT was the first task tested in these rats, in which they were required to make a right or left turn toward the arm of the maze where the visual cue was placed to obtain rewards (a piece of cereal). After performance criterion was reached (ten consecutive

correct responses in one session; one session consisted of 12 trials; two sessions were given per day), the task was switched to RDT in which animals always had to make a left or right turn, regardless of the visual cue placed in the arms of the maze to obtain rewards, and sessions were continued until performance criterion was reached. Perseverative errors, which are the errors associated with switching to new strategy, were defined as the number of error trials until animals made the first correct turn in the trial in which the visual cue was placed in the arm opposite to the direction of the turn. Regressive errors, which are the errors associated with learning a new strategy, were defined as the number of error trials that animals made toward the visual cue in the maze, but after a first correct trial in RDT.

Acknowledgments

We thank Ms. N. Macmurdo and C. Smolak for technical assistance; Mr. B. Lowry for data acquisition software; Drs. A. West and M. Takita for suggestions on reverse microdialysis technique; Dr. S. Otani for helpful comments on the manuscript; and Dr. A.M. Graybiel for reading the manuscript. This work was supported by USPHS MH57440 (A.A.G.) and National Alliance for Research on Schizophrenia and Depression Young Investigator Award (Y.G.). Y.G. is a NARSAD Essel Investigator.

Received: November 23, 2004
Revised: January 20, 2005
Accepted: June 17, 2005
Published: July 20, 2005

References

Bamford, N.S., Zhang, H., Schmitz, Y., Wu, N.P., Cepeda, C., Levine, M.S., Schmauss, C., Zakharenko, S.S., Zablow, L., and Sulzer, D. (2004). Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals. Neuron *42*, 653–663.

Berridge, K.C., and Robinson, T.E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Brain Res. Rev. *28*, 309–369.

Bissiere, S., Humeau, Y., and Luthi, A. (2003). Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. Nat. Neurosci. *6*, 587–592.

Calabresi, P., Maj, R., Mercuri, N.B., and Bernardi, G. (1992). Coactivation of D1 and D2 dopamine receptors is required for long-term synaptic depression in the striatum. Neurosci. Lett. *142*, 95–99.

Ciccocioppo, R., Sanna, P.P., and Weiss, F. (2001). Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D(1) antagonists. Proc. Natl. Acad. Sci. USA *98*, 1976–1981.

Degenetais, E., Thierry, A.M., Glowinski, J., and Gioanni, Y. (2003). Synaptic influence of hippocampus on pyramidal cells of the rat prefrontal cortex: an in vivo intracellular recording study. Cereb. Cortex *13*, 782–792.

Della-Maggiore, V., Sekuler, A.B., Grady, C.L., Bennett, P.J., Sekuler, R., and McIntosh, A.R. (2000). Corticolimbic interactions associated with performance on a short-term memory task are modified by age. J. Neurosci. *20*, 8410–8416.

Drevets, W.C. (2000). Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog. Brain Res. *126*, 413–431.

Finch, D.M. (1996). Neurophysiology of converging synaptic inputs from the rat prefrontal cortex, amygdala, midline thalamus, and hippocampal formation onto single neurons of the caudate/putamen and nucleus accumbens. Hippocampus *6*, 495–512.

Floresco, S.B., Blaha, C.D., Yang, C.R., and Phillips, A.G. (2001a). Dopamine D1 and NMDA receptors mediate potentiation of basolateral amygdala-evoked firing of nucleus accumbens neurons. J. Neurosci. *21*, 6370–6376.

Floresco, S.B., Todd, C.L., and Grace, A.A. (2001b). Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. J. Neurosci. *21*, 4915–4922.

Floresco, S.B., West, A.R., Ash, B., Moore, H., and Grace, A.A. (2003). Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat. Neurosci. *6*, 968–973.

French, S.J., and Totterdell, S. (2002). Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. J. Comp. Neurol. *446*, 151–165.

Fuster, J.M. (1997). The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe, Third Edition (Philadelphia: Lippincott-Raven).

Gilboa, A., Shalev, A.Y., Laor, L., Lester, H., Louzoun, Y., Chisin, R., and Bonne, O. (2004). Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. Biol. Psychiatry *55*, 263–272.

Goto, Y., and Grace, A.A. (2005). Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat. Neurosci. *8*, 805–812.

Goto, Y., and O'Donnell, P. (2002). Timing-dependent limbic-motor synaptic integration in the nucleus accumbens. Proc. Natl. Acad. Sci. USA *99*, 13189–13193.

Grace, A.A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience *41*, 1–24.

Greengard, P., Allen, P.B., and Nairn, A.C. (1999). Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. Neuron *23*, 435–447.

Groenewegen, H.J., Wright, C.I., Beijer, A.V., and Voorn, P. (1999). Convergence and segregation of ventral striatal inputs and outputs. Ann. N Y Acad. Sci. *877*, 49–63.

Gurden, H., Tassin, J.-P., and Jay, T.M. (1999). Integrity of the mesocortical dopaminergic system is necessary for complete expression of in vivo hippocampal-prefrontal cortex long-term potentiation. Neuroscience *94*, 1019–1027.

Hall, H., Kohler, C., and Gawell, L. (1985). Some in vitro receptor binding properties of [3H]eticlopride, a novel substituted benzamide, selective for dopamine-D2 receptors in the rat brain. Eur. J. Pharmacol. *111*, 191–199.

Hyman, S.E., and Malenka, R.C. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. Nat. Rev. Neurosci. *2*, 695–703.

Jackson, M.E., Frost, A.S., and Moghaddam, B. (2001). Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J. Neurochem. *78*, 920–923.

Jentsch, J.D., and Taylor, J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl.) *146*, 373–390.

Knight, R.T., and Grabowecky, M. (1999). Prefrontal cortex, time, and consciousness. In The New Cognitive Neuroscineces, M.S. Gazzaniga, ed. (Cambridge, MA: MIT Press), pp. 1319–1339.

Kolb, B., Gorny, G., Li, Y., Samaha, A.N., and Robinson, T.E. (2003). Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens. Proc. Natl. Acad. Sci. USA *100*, 10523–10528.

Kombian, S.B., and Malenka, R.C. (1994). Simultaneous LTP of non-NMDA- and LTD of NMDA-receptor-mediated responses in the nucleus accumbens. Nature *368*, 242–246.

Kyd, R.J., and Bilkey, D.K. (2003). Prefrontal cortex lesions modify the spatial properties of hippocampal place cells. Cereb. Cortex *13*, 444–451.

Laruelle, M., Kegeles, L.S., and Abi-Dargham, A. (2003). Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. Ann. N Y Acad. Sci. *1003*, 138–158.

Lawrie, S.M., Buechel, C., Whalley, H.C., Frith, C.D., Friston, K.J., and Johnstone, E.C. (2002). Reduced frontotemporal functional

connectivity in schizophrenia associated with auditory hallucinations. Biol. Psychiatry *51*, 1008–1011.

Mangiavacchi, S., and Wolf, M.E. (2004). Stimulation of N-methyl-D-aspartate receptors, AMPA receptors or metabotropic glutamate receptors leads to rapid internalization of AMPA receptors in cultured nucleus accumbens neurons. Eur. J. Neurosci. *20*, 649–657.

Milner, B. (1963). Effects of different brain lesions on card sorting. Arch. Neurol. *9*, 90–100.

Mulder, A.B., Arts, M.P., and Lopes da Silva, F.H. (1997). Short- and long-term plasticity of the hippocampus to nucleus accumbens and prefrontal cortex pathways in the rat, in vivo. Eur. J. Neurosci. *9*, 1603–1611.

O'Donnell, P., and Grace, A.A. (1994). Tonic D2-mediated attenuation of cortical excitation in nucleus accumbens neurons recorded in vitro. Brain Res. *634*, 105–112.

Opitz, B., and Friederici, A.D. (2003). Interactions of the hippocampal system and the prefrontal cortex in learning language-like rules. Neuroimage *19*, 1730–1737.

Otmakhova, N.A., and Lisman, J.E. (1999). Dopamine selectively inhibits the direct cortical pathway to the CA1 hippocampal region. J. Neurosci. *19*, 1437–1445.

Pennartz, C.M., Ameerun, R.F., Groenewegen, H.J., and Lopes da Silva, F.H. (1993). Synaptic plasticity in an in vitro slice preparation of the rat nucleus accumbens. Eur. J. Neurosci. *5*, 107–117.

Ragozzino, M.E., Ragozzino, K.E., Mizumori, S.J., and Kesner, R.P. (2002). Role of the dorsomedial striatum in behavioral flexibility for response and visual cue discrimination learning. Behav. Neurosci. *116*, 105–115.

Robinson, T.E., and Kolb, B. (1999). Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. Eur. J. Neurosci. *11*, 1598–1604.

Rosenkranz, J.A., Moore, H., and Grace, A.A. (2003). The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. J. Neurosci. *23*, 11054–11064.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. J. Neurophysiol. *80*, 1–27.

Seamans, J.K., Floresco, S.B., and Phillips, A.G. (1998). D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J. Neurosci. *18*, 1613–1621.

Sesack, S.R., and Carr, D.B. (2002). Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. Physiol. Behav. *77*, 513–517.

Silbersweig, D., and Stern, E. (1996). Functional neuroimaging of hallucinations in schizophrenia: toward an integration of bottom-up and top-down approaches. Mol. Psychiatry *1*, 367–375.

Simons, J.S., and Spiers, H.J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. Nat. Rev. Neurosci. *4*, 637–648.

Stanton, P.K., Winterer, J., Bailey, C.P., Kyrozis, A., Raginov, I., Laube, G., Veh, R.W., Nguyen, C.Q., and Muller, W. (2003). Long-term depression of presynaptic release from the readily releasable vesicle pool induced by NMDA receptor-dependent retrograde nitric oxide. J. Neurosci. *23*, 5936–5944.

Thomas, M.J., Malenka, R.C., and Bonci, A. (2000). Modulation of long-term depression by dopamine in the mesolimbic system. J. Neurosci. *20*, 5581–5586.

Thomas, M.J., Beurrier, C., Bonci, A., and Malenka, R.C. (2001). Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. Nat. Neurosci. *4*, 1217–1223.

Voorn, P., Jorritsma-Byham, B., Van Dijk, C., and Buijs, R.M. (1986). The dopaminergic innervation of the ventral striatum in the rat: a light- and electron-microscopical study with antibodies against dopamine. J. Comp. Neurol. *251*, 84–99.

Vorel, S.R., Liu, X., Hayes, R.J., Spector, J.A., and Gardner, E.L. (2001). Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science *292*, 1175–1178.

Wall, P.M., and Messier, C. (2001). The hippocampal formation—orbitomedial prefrontal cortex circuit in the attentional control of active memory. Behav. Brain Res. *127*, 99–117.

West, A.R., and Grace, A.A. (2002). Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining in vivo intracellular recordings and reverse microdialysis. J. Neurosci. *22*, 294–304.

Wise, R.A. (2004). Dopamine, learning and motivation. Nat. Rev. Neurosci. *5*, 483–494.